REMARKS

Favorable reconsideration of the subject application is respectfully requested in view of the above amendments and the following remarks. Claims 1-112 are pending in the instant application, and claims 1-4, 8-26, and 30-41 are currently under consideration. Claims 1, 4, 8, 20, 26, 36, 37 and 40 have been amended to more particularly point out and distinctly claim certain embodiments of the invention, and claims 5-7, 27-29, and 42-112 have been canceled. Support for these amendments may be found throughout the specification and claims as originally filed, and it is urged that the amendments do not constitute new matter. Support for human ANT3 variants having at least 95% identity to SEQ ID NO:33 is provided, *e.g.*, at page 24, lines 4-6. It should also be noted that the above amendments are not to be construed as acquiescence with regard to the PTO's rejections and are made without prejudice to prosecution of any subject matter removed or modified by this amendment in a related divisional, continuation or continuation-in-part application.

RESPONSE TO RESTRICTION REQUIREMENT

In response to the restriction requirement, Applicants hereby elect Group III, claims 1-4, 7-26, and 29-41, drawn to recombinant expression constructs encoding an ANT3 polypeptide, classified in class 435, subclass 320.1, for examination at this time.

OBJECTION TO THE DISCLOSURE

The PTO objects to the disclosure for allegedly containing informalities by not providing sequence identifiers for the sequences listed in Figures 1A, 1B, and 2.

Applicants have amended the Brief Description of the Drawings to reference the appropriate sequence identifiers, as indicated above. Applicants respectfully request that this objection be withdrawn in light of the present amendment.

REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 4, 20-26, 30-38, and 40-41 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

Specifically, claims 36 and 37 are alleged to be unclear in their reference to a host cell according to claim 20, where claim 20 is directed to a recombinant expression construct. Applicants thank the Examiner for bringing this typographical error to their attention and note that the reference to claim 20 was a typographical error which has been corrected by the present amendment; claims 36 and 37 now correctly refer instead to claim 31.

Claims 4, 20, 26, and 40 (and dependent claims 21-25, 30-38, and 41) are alleged to be unclear in their recitations of "animal" or "human" adenine nucleotide translocator, as the PTO asserts that the metes and bounds of such polypeptides are unclear.

Applicants respectfully traverse this rejection and submit that claims 4, 20, 26, and 40, as amended herewith without acquiescence in any rejection asserted by the PTO, are directed in pertinent part to recombinant expression constructs encoding polypeptides having at least 95% identity to a human ANT3 polypeptide comprising the amino acid sequence set forth in SEQ ID NO:33. Applicants submit that the metes and bounds of the recited polypeptides encoded by the expression constructs as presently encompassed by claims 4, 20, 26 and 40 (and dependent claims 21-25, 30-38, and 41) are now abundantly clear.

In view of the foregoing, Applicants submit that the present application satisfies all requirements of 35 U.S.C §112, second paragraph, and therefore respectfully request that these rejections be withdrawn.

REJECTIONS UNDER 35 U.S.C. § 103

Claims 1-4, 8-17, 20-26, 30-35, and 38-41 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Krief *et al.* (U.S. Patent No. 6,316,219) in view of Ausubel *et al.* (Short Protocols in Molecular Biology, 3rd Ed., 1997, John Wiley & Sons, New York, Chapter 13, pp. 26-35 and Chapter 16, pp. 1-7, 16-23, 25-31, 37-54, 58-62). More specifically, the PTO alleges that Krief *et al.* teach an expression construct comprising a nucleic acid molecule

encoding human ANT5 or a fusion protein thereof, host cells, and methods of making a recombinant human ANT5 using the described expression system. The PTO concedes that Krief *et al.* do not teach the use of a regulated promoter, the use of a nucleic acid sequence encoding a repressor, or the use of a second nucleic acid sequence encoding an enzyme cleavable by a protease. The PTO asserts, however, that Ausubel *et al.* teach that inducible promoters and repressors, and fusion proteins cleavable by a protease and comprising an enzyme, were widely available and known to those of ordinary skill in the art at the time of the invention. The PTO asserts further that it would have been obvious to express the ANT5 sequence disclosed by Krief *et al.* using the methods described in Ausubel *et al.* The PTO also asserts that the skilled artisan would have been motivated to use an inducible promoter and repressor, as suggested by Krief *et al.*, to minimize toxicity, since it was understood that overexpression of membrane proteins can be toxic. In addition, it is asserted in the Action that the skilled artisan would have been motivated to use an expression construct encoding an ANT5 fusion protein comprising a cleavable enzyme, in order to facilitate expression and recovery.

Applicants respectfully traverse this rejection and submit that the cited publications, alone or in combination, fail to teach or suggest combining each element of the invention as presently claimed, and thus fail to render the claimed invention obvious. Applicants note that in order for the PTO to establish *prima facie* obviousness of a claimed invention, all the claim elements must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981 (CCPA 1974). Briefly, with respect to the instant claims and for reasons discussed in greater detail below and in the Declaration of Dr. Christen Anderson enclosed herewith, the prior art fails even remotely to suggest that the problem of expressing a recombinant adenine nucleotide translocator polypeptide can be overcome by using a recombinant expression construct comprising at least one regulated promoter operably linked to a nucleic acid encoding the ANT polypeptide, as provided by the present invention.

Claims 1, 20, and 40, as amended herewith solely to expedite prosecution of the instant application and without acquiescence to this or any other rejection, are directed in pertinent part to a recombinant expression construct comprising a nucleic acid that encodes a polypeptide having at least 95% sequence identity to a human ANT3 polypeptide comprising the sequence set forth in SEQ ID NO:33. Applicants submit that the cited documents fail to teach or

suggest a recombinant expression construct encoding such a polypeptide, and that therefore the instant claims cannot be obvious over this combination of publications.

Claims 7 and 29 stand rejected under 35 U.S.C. § 103(a), as allegedly obvious over Krief *et al.* (U.S. Patent No. 6,316,219) and Ausubel *et al. (supra)* as applied above, and further in view of Cozens *et al.* (1989 *J. Mol. Biol.* 206:261). The PTO acknowledges that neither Krief *et al.* nor Ausubel *et al.* disclose the DNA or amino acid sequence of ANT3. However, the Action alleges that Cozens *et al.* teach the human ANT3 DNA sequence. The PTO then asserts that it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the methods of Krief *et al.* and Ausubel *et al.* to make an expression vector encoding ANT3, using the sequence taught by Cozens *et al.* In addition, the PTO asserts that the skilled artisan would have been motivated to do so in order to produce large amounts of ANT3 for localization and functional studies. Applicants respectfully traverse this rejection and point out that it is rendered moot by the cancellation of claims 7 and 29 according to the amendment submitted herewith.

Claims 18, 19, and 36-37 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Krief *et al.* and Ausubel *et al.*, as applied above, and further in view of LeSaux *et al.* (1996 *Biochemistry* 35:16116) and Wallace *et al.* (WO 98/19714). The PTO concedes that Krief *et al.* and Ausubel *et al.* fail to disclose a host cell lacking at least one isoform of an endogenous ANT. However, the PTO asserts that LeSaux *et al.* describe a yeast cell that lacks all isoforms of ANT except for ANC2, and further asserts that Wallace *et al.* provide evidence that animal cells can be made wherein an individual ANT gene is impaired, such that the host cell lacks the ANT isoform encoded by the impaired gene. The PTO then alleges that it would have been obvious to the skilled artisan to modify a host cell comprising an inducible expression construct encoding an ANT polypeptide, as taught in Krief *et al.* and Ausubel *et al.*, such that the host cell lacks at least one endogenous isoform of ANT, as described by Le Saux *et al.* and Wallace *et al.* The Action asserts that one would have been motivated to do so in order to study an individual ANT isoform, or to study the effect of the deficiency of a particular ANT isoforms on cellular function.

Applicants respectfully traverse these grounds for rejection and submit that the PTO fails to establish a *prima facie* case of obviousness in light of the combination of cited

publications. The present invention relates in pertinent part to a recombinant expression construct comprising a regulated promoter operably linked to a nucleic acid encoding a human adenine translocator polypeptide 3 (ANT3) polypeptide comprising the amino acid sequence set forth in SEQ ID NO:33, or having at least 95% sequence identity to SEQ ID NO:33. Applicants submit that nowhere in any of the documents cited by the PTO can there be found any teaching or suggestion to combine these publications to arrive at the claimed invention, nor has the PTO provided any evidence that an ordinarily skilled artisan would have been motivated to do so with the requisite reasonable expectation of success. Applicants submit that even assuming *arguendo* that each element of the presently claimed invention was described in the cited documents, the mere fact that the teachings of the prior art *can* be combined or modified, or that a person having ordinary skill in the art is *capable* of combining or modifying the teachings of the prior art, does not make the resultant combination *prima facie* obvious, as the prior art must also suggest the desirability of the combination (*see, e.g., In re Mills*, 16 USPQ2d 1430, Fed. Cir. 1990; *In re Fritch*, 23 USPQ2d 1780, Fed. Cir. 1992).

With regard to any of the claims rejected by the PTO under 35 U.S.C. § 103, the PTO concedes that Krief *et al.* fail to describe the use of a regulatable promoter in an ANT expression construct. Cozens *et al.* merely disclose ANT encoding polynucleotide sequences but fail to describe any ANT expression construct, nor do Cozens *et al.* in any way suggest that it would be desirable for an ANT expression construct to comprise a regulated promoter. Applicants submit further that Ausubel *et al.* are silent with regard to the problem of recombinant ANT expression, and thus also fail to suggest the desirability of using a regulatable promoter in an ANT expression construct. Applicants submit that taken together, the cited publications fail to suggest the desirability of combining their teachings to achieve the presently claimed invention, and that in alleging obviousness of the claimed invention over these documents, the PTO employs impermissible hindsight given the instant application.

In addition, Applicants disagree with the PTO's conclusion that the skilled artisan would have been motivated to combine the teachings of the prior art to achieve the presently claimed recombinant expression constructs. Applicants submit that the skilled artisan would understand that the recombinant production of human ANT polypeptides has historically been very difficult, if not impossible, as discussed in the accompanying Declaration of Dr. Christen

M. Anderson. Applicants further submit that Krief *et al.* merely suggest a *potential* human ANT5 expression construct, *i.e.*, incorporation of the ANT5 encoding sequence described therein into a standard expression vector. Krief *et al.* absolutely do not, however, provide any evidence whatsoever showing actual assembly of a human ANT5 expression construct that is used successfully to produce recombinant human ANT5 polypeptide, nor (for reasons discussed above) can Krief *et al.* be combined with the other cited documents to create an expectation of successfully producing any recombinant human ANT. Accordingly, Applicants submit that absent a working model and in light of the historical difficulties associated with expressing and isolating human ANT polypeptides (as also discussed in the Anderson Declaration), a person having ordinary skill in the art would not reasonably have expected successfully to express human ANT3 using the expression constructs of the present invention, given only the general description of a theoretical human ANT5 expression construct that Krief *et al.* provide, even with the sequences of Cozens *et al.* and the general teachings of Ausubel *et al.* Therefore, the PTO has not established a *prima facie* case of obviousness where it cannot be demonstrated that at the time of filing the instant application, the ordinarily skilled artisan would have been motivated to combine the cited publications to arrive at the present invention.

In particular with regard to the rejection of claims 18-19 and 36-37, and for reasons also set forth above, the Action fails to establish that the skilled artisan would have had any motivation to combine Krief *et al.* and Ausubel *et al.* to achieve an expression construct comprising a regulatable promoter operably linked to a nucleic acid encoding a polypeptide having at least 95% identity to a human ANT3 polypeptide comprising the sequence set forth in SEQ ID NO:33. Applicants further submit that Le Saux *et al.* and Wallace *et al.* fail to remedy this deficiency in the combination of Krief *et al.* and Ausubel *et al.*, because any combination of the cited publications simply fails to teach or suggest the desirability of combining the disclosures found therein to achieve a host cell comprising the subject invention expression construct. Furthermore, Applicants submit that none of the cited documents teaches or suggests the desirability of producing a host cell that comprises a recombinant expression construct as presently claimed, and that lacks an endogenous ANT isoform (claims 18 and 36), or in which host cell expression of at least one gene encoding an ANT isoform is substantially impaired

(claims 19 and 37), as also presently claimed. Accordingly, Applicants submit that a *prima facie* case of obviousness has not been established in light of the combination of cited publications.

In addition to the above remarks specifically traversing each of the rejections asserted by the PTO under 35 U.S.C. § 103(a), Applicants also respectfully submit that the present invention is nonobvious when "secondary factors," including, in particular, the identification of a long-felt need and the failure of others, are considered. It is well established that considerations such as long-felt but unsolved needs, and the failure of others to arrive at Applicants' invention, are not only relevant to the obviousness inquiry, but must be considered when present. *Custom Accessories Inc., v. Jeffrey-Allan Industries Inc.*, 807 F.2d 955; 1 USPQ2d 1196 (Fed. Cir. 1986); *Ryko Manufacturing Co. v. Nu-Star Inc.*, 950 F.2d 714, 21 USPQ2d 1053, 1057 (Fed. Cir. 1991).

As evidence of the existence of secondary factors demonstrating that the present invention was not obvious at the time of filing the instant application, Applicants submit herewith the Declaration of Dr. Christen M. Anderson (as also previously submitted in copending U.S. patent application Serial No. 09/185,904) which Declaration presents evidence of the importance of ANT polypeptides in human disease, the long-felt need for recombinant ANT polypeptides for additional research, and the unsuccessful attempts by other investigators to produce recombinant ANT polypeptides. In light of the Declaration, Applicants respectfully submit that cDNA sequences encoding a human ANT polypeptide were known as early as 1987, and recombinant protein expression methods were established well before 1987. In addition, the desirability of expressing a functional ANT polypeptide is clearly evidenced by the attention directed to ANT polypeptides by numerous investigators, as indicated by the references cited throughout the instant specification. Accordingly, Applicants submit that a long-felt need for recombinant expression constructs capable of expressing isolatable ANT polypeptides was present at the time of filing the parent of the instant application in 1998. Moreover, Applicants are unaware of any successful production by others of a functional isolated recombinant human ANT polypeptide. In view of the absence of any such disclosures in the prior art, and further in view of the unsuccessful efforts of others to express and isolate recombinant ANT polypeptides, as described in the Declaration, Applicants respectfully submit that the present invention is nonobvious in light of the long-felt need for expression constructs capable of expressing

isolatable recombinant ANT polypeptides and fusion proteins, which long-felt need remained unmet prior to the present invention.

In view of the foregoing, Applicants respectfully submit that the PTO has not established a *prima facie* case of obviousness. Applicants submit that the documents cited by the PTO fail to teach or suggest each element of the claimed invention, and also fail to provide a suggestion or motivation to a person having ordinary skill in the art to modify or combine any prior art teachings to arrive at the claimed invention with a reasonable expectation of success. Additionally, and as also discussed above, secondary considerations clearly indicate that the invention is non-obvious. Accordingly, Applicants submit that the invention satisfies the requirements of 35 U.S.C. §103 and respectfully request that these rejections be withdrawn.

Additionally, applicants wish to call the Examiner's attention to several related co-pending applications having claims potentially directed to similar subject matter. Reference to the appended "Table of Co-Pending Applications" is therefore requested.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

All of the claims remaining in the application are now clearly allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

Christen M. Anderson et al.

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Enclosures:
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APPENDIX: TABLE OF CO-PENDING APPLICATIONS

U.S.A.N.	Atty. Docket No.	Examiner	Claims directed to ____ (Comments)
09/393,441	660088.420C1	Sheridan Snedden	__ isolated recombinant huANT3 polypeptide that localizes to mitochondrial membrane Statutory double-patenting rejection of claims 42, 46-48, 51 and 57 over claims 42, 46-48,51 and 57 of 09/185,904
09/185,904	660088.420	Holly G. Schnizer	__ isolated recombinant huANT3 polypeptide Obviousness-type double patenting rejection of claims 42, 46-50 over claims 42, 46-48, 51 and 57 of 09/393,441
09/811,131	660088.420D1	Holly G. Schnizer	__ method of identifying agent that binds to ANT polypeptide
09/811,185	660088.420D2	Rebecca L. Anderson	__ method of treatment using ANT ligand
09/810,644	660088.420D3	Rebecca L. Anderson	__ ANT ligand
09/811,094 (present application)	660088.420D4	Holly G. Schnizer	__ recombinant expression construct, host cell, and method of making recombinant ANT polypeptides and fusion proteins
09/811,132	660088.420D5	Holly G. Schnizer	__ methods of detecting and isolating an ANT polypeptide, using ANT ligand
09/809,827	660088.420D6	Holly G. Schnizer	__ isolated recombinant huANT1 polypeptide
09/809,889	660088.420D7	Holly G. Schnizer	__ isolated recombinant huANT2 polypeptide
09/569,327	660088.443	Sheridan Snedden	__ method of producing recombinant ANT polypeptides and fusion proteins using tightly regulated promoter
10/684,232	660088.433C2	(none assigned)	__ANT-energy transfer peptide fusion proteins